REVIEW PAPER

 New Med 2016; 20(1): 27-29 DOI: 10.5604/14270994.1197178

PATHOPHYSIOLOGY OF RENAL BLOOD SUPPLY

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Summary
Acute kidney injury has an increasing incidence and high mortality rate with enormous financial and healthcare implications. The pathophysiology differs in various clinical situations (e.g. sepsis, cardiac arrest or other low flow states, cardiorenal and hepatorenal syndromes etc.), but the impaired blood supply plays an important role in destroying renal function. Unfortunately, despite of the multiple technical possibilities, monitoring of renal blood flow is unavailable in clinical practice, because of the high personal and environmental demand of the measurements. One should always remind himself of the fact, that the net filtration pressure in glomeruli is about 10 mmHg in physiological circumstances. Kidneys are in the vessel-rich group of organs with brain, heart and liver, therefore receive a very high amount of cardiac output (about 20%) with relatively low oxygen extraction rate (10%). Equally, the decreased arterial flow, the intrarenal imbalance and the venous side anomalies can cause renal failure. We would like to show a holistic picture from the pathophysiology of renal circulation.

Keywords: acute renal failure, acute kidney injury, renal blood flow, sepsis, heart failure

INTRODUCTION

The occurrence of acute kidney injury (AKI) dramatically increases the mortality rate in intensive care unit either in septic or postoperative patients. This fact has not been changed with the development of renal replacement techniques, therefore the prevention of AKI is very important. The understanding the physiology of renal blood supply in normal and in pathological circumstances is essential for doing the best clinical practice. Although the change of glomerular arterial resistances has been investigated in most studies, increasing amount of evidences supports the role of venous factors. The aim of our work was to review the clinically relevant data.

PHYSIOLOGY OF THE RENAL CIRCULATION

Renal blood flow (RBF) takes normally approximately 20% of cardiac output, which is 10-50 times greater than other organs regarding their weight (1, 2). The glomerular effective filtration pressure depends on the mean capillary pressure (normally 45 mmHg), opposing the intracapsular/interstitial pressure (10 mmHg) and the mean colloid osmotic pressure (25 mmHg). Therefore physiologically the net filtration pressure gradient is about 10 mmHg. Any change in the colloid and hydrostatic pressures changes the number of filtrating glomeruli or the surface area serving as functional reserve capacity. A major determinant of the glomerular filtration rate (GFR) is the glomerular pressure depending on the balance between afferent and efferent arteriolar resistance. Regulation of RBF comes from factors (1) that are both extrarenal (sympathic nerves, circulating agents, e.g. renin-angiotensin II-aldosteron system, nor/epinephrine thromboxane, 20-hydroxyeicosatetraenoic acid, prostacyclin) and intrarenal (preglomerular arterial myogenic response, tubuloglomerular feedback, nitric oxide, endothelium-derived hyperpolarizing factor). The unimpaired autoregulatory mechanism keeps the GFR constant in a wide range of mean arterial pressures (MAP).

Renal oxygen consumption is 10 ml/min/100 g but the extraction ratio from the oxygen supply is quite low (10% in the kidneys vs. 55% in the heart). The reason for this is that RBF comprises a relatively high proportion of cardiac output (3, 4). The highest oxygen-dependent intrarenal process is the tubular reabsorption of sodium. Increasing RBF normally raises the GFR and tubular sodium load, so that renal oxygen extraction remains the same over a wide range of RBF. The partial pressure of oxygen in the kidneys is different. It is 10-20 mmHg in the outer medulla compared to 50 mmHg in the cortex, due to the regional distribution of blood supply.

GLOMERULAR PATHOPHYSIOLOGY

The kidney in SIRS/sepsis

The sepsis-associated AKI (SA-AKI) seems to be inflammatory and ischaemic in origin. In experimental sepsis with hyperkinetic circulation the GFR decreased and AKI

occurred even though the RBF was undiminished (5, 6). In human studies the RBF increased in sepsis, and the only significant predictor of this was cardiac output (7, 8). In other studies it was reported that the proportion of RBF decreased from the normal 20% to 7% of cardiac output (8). The renal autoregulation is impaired either in sepsis or in AKI, respectively (9-11). The consequence of this impairment is vasodilatation (partially) caused by nitric oxide resulting cardiac output dependency of RBF. Interestingly, inhibiting the nitric oxide synthase did not influence the kidney injury in sheep (6, 11). Vasodilatation favors the efferent arteriolae, and together with the myogenic increase in the afferent arteriolar resistance leads to the deterioration of glomerular ultrafiltration.

Furthermore, in sepsis the intrarenal microcirculation distribution is altered exposing the medulla to ischaemic risk and tubular dysfunction, as measured by Doppler flowmetry (6). In different septic animal models the occurrence of capillary leakage precedes the changes in RBF, indicating the role of local inflammatory processes. Despite decreasing RBF, tissue oxygen tension is maintained, mitochondrial respiration is undisturbed and renal adenosine triphosphat levels are sustained – however renal function fails. In ischaemic animal models, unclamping resolves the RBF, but later on it once more decreases in spite of physiological macrocirculation implicating intrarenal factors. Many other nonvascular processes seem to be taking place in SA-AKI, e.g. tubuloglomerular feedback activation, tubular obstruction and tubular back-leakage. The predictor of sustained AKI is elevated tubular and intracapsular pressure.

Cardiorenal and hepatorenal syndromes

The insufficiency of heart and/or kidney function can lead to a worsening of both. In current terminology there are five subtypes of cardiorenal syndrome (CRS), according to the primary lesion and its duration. As regards CRS 1, the most widely accepted theory most is the low-flow state hypothesis. This hypothesis is not supported by the results of the prospective ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) revealing a positive correlation between the elevated central venous/right atrial pressure and renal failure. They were independent predictors of mortality and hospitalization, while cardiac index did not show any correlation with the renal function (12).

In respect of the hepatorenal syndrome, three major theories exist: the overflow, the underfilling and the peripheral arterial vasodilatation hypotheses (13, 14). The overflow mechanism means increasing portal vascular resistance and renal vasoconstriction by activating hepatorenal reflex. It results in sodium and water retention, expansion of circulating blood volume and overflow of fluid to the peritoneal space. The underfilling theory highlights the augmentation of splanchnic lymph production as a result of the growing splanchnic but decreasing systemic blood volume and subsequent stimulation of the renin-angiotensin system. According to the third and the most popular possible pathomechanism, the main problem is the peripheral arterial vasodilatation with reactive stimulation of secreted vasoconstrictor agents and renal vasoconstriction as sequelae. The RAAS, the sympathetic nervous system and inducible nitric oxide synthase play a central role in this syndrome (14).

VENOUS AND LYMPHATIC FACTORS

In a healthy person, elevated right atrial pressure increases the release of vasopressin and atrial natriuretic peptides, and lowers the renal sympathetic tone. In heart failure these mechanisms are suppressed and despite the raised venous pressure sodium and water retention are detected. The kidney is an encapsulated organ, which means the augmentation of interstitial pressure above a certain range becomes much steeper. The first animal data from 1931, followed by the first human study conducted in 1948, suggested that increasing venous pressure causes a deterioration in renal function similar to that resulting from a decrease of arterial pressure (2, 15, 16).

According to the animal data, the splanchnic venous system encompasses 25% of the total blood volume and can buffer 65% more fluid added to the euvolemic status without any change in macrocirculatory parameters (17, 18). In septic patients at CVP of 6 mmHg the incidence of AKI is 30%, and at CVP of 15 mmHg it is 80% (19, 20). In heart failure the raised venous pressure is an independent risk factor for decreasing glomerular filtration (21).

Several data prove the role of intraabdominal hypertension in the developing of AKI (22-24). Renal perfusion pressure (RPP) is computed from MAP-IAP (intraabdominal pressure), and the filtrating gradient (FG) from RPP-IAP based on mostly animal data (24). Critically ill patients in shock, in elevated IAP (regarding 12 mmHg as best cut-off level), and having low abdominal perfusion pressure, had the highest predictive value for AKI (23). In 60% of patients with congestive heart disease the IAP exceeds the physiological 5-7 mmHg, and also in the range of 8-12 mmHg can be detected renal impairment (25).

In 145 patients suffering from severe cardiac decompensation the incidence of AKI was higher in the subgroup with higher CVP (18 ± 7 mmHg vs. 12 ± 6 mmHg, $p < 0.001$) and when it remained resistant to therapeutic efforts (26). The best outcome was in patients with CVP < 8 mmHg. In another 17-year study of 2,557 patients who had undergone right heart catheterization, the correlation between CVP and eGFR remained, even after multivariate logistic regression analysis (27). This relationship was independent of the cardiac index. The worsening of renal function occurred above CVP of 6 mmHg.

Mechanical ventilation alone correlates with the incidence of AKI, but the efforts to identify predictive pressure or volume parameters have remained unsuccessful (28).

DISCUSSION

In this paper we have tried to review renal hemodynamics in all its complexity. To the best of our knowledge previous studies have discussed the inflow of blood to the renal vascular bed and the change of intrarenal arterial resistances, but the outflow of blood has remained outside their scope. In the cardiological literature the possible role of venous pressure in the pathophysiology of renal dysfunction has been discussed. It seems to be important not only in the development of cardiorenal syndromes, but in sepsis associated acute kidney injury as well. This clearly has enormous financial and healthcare implications.

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Conflict of interest
None

Received: 02.11.2015
Accepted: 04.01.2016